

WE CLAIM:

1. A conjugate consisting essentially of one or more antibody fragments covalently attached to one or more nonproteinaceous polymer molecules, wherein the apparent size of the conjugate is at least about 500 kD, and wherein at least one antibody fragment comprises an antigen binding site that binds to a polypeptide selected from the group consisting of: human vascular endothelial growth factor (VEGF), human p185 receptor-like tyrosine kinase (HER2), human CD20, human CD18, human CD11a, human IgE, human Apo-2 receptor, human tumor necrosis factor- α (TNF- α), human tissue factor (TF), human $\alpha 4\beta 7$ integrin, human GPIIb-IIIa integrin, human epidermal growth factor receptor (EGFR), human CD3, and human interleukin-2 receptor α -chain (TAC).

2. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 800 kD.

3. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 1,400 kD.

4. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 1,800 kD.

5. The conjugate of claim 1, wherein the apparent size of the conjugate is at least about 8 fold greater than the apparent size of at least one antibody fragment.

6. The conjugate of claim 5, wherein the apparent size of the conjugate is at least about 15 fold greater than the apparent size of at least one antibody fragment.

7. The conjugate of claim 6, wherein the apparent size of the conjugate is at least about 25 fold greater than the apparent size of at least one antibody fragment.

8. The conjugate of claim 1, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab', Fab'-SH, Fv, scFv and F(ab')₂.

9. The conjugate of claim 8 wherein the antibody fragment is F(ab')₂.

10. The conjugate of claim 1 wherein at least one antibody fragment is covalently attached to no more than about 10 nonproteinaceous polymer molecules.

11. The conjugate of claim 10 wherein the antibody fragment is covalently attached to no more than about 5 nonproteinaceous polymer molecules.

12. The conjugate of claim 11 wherein the antibody fragment is covalently attached to no more than about 2 nonproteinaceous polymer molecules.

13. The conjugate of claim 12 wherein the antibody fragment is attached to no more than 1 nonproteinaceous polymer molecule.

14. The conjugate of claim 12, wherein the antibody fragment comprises a heavy chain and a light chain derived from a parental antibody, wherein in the parental antibody the heavy and light chains are covalently linked by a disulfide bond between a cysteine residue in the light chain and a cysteine residue in the heavy chain, wherein in the antibody fragment the cysteine residue in the light or heavy chain is substituted with another amino acid and the cysteine residue in the opposite chain is covalently linked to a nonproteinaceous polymer molecule.

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15. The conjugate of claim 8 wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH.

5 16. The conjugate of claim 15 wherein the antibody fragment is covalently attached to no more than 1 nonproteinaceous polymer molecule.

17. The conjugate of claim 16 wherein the nonproteinaceous polymer molecule in the conjugate is covalently attached to the hinge region of the antibody fragment.

10 18. The conjugate of claim 1 wherein at least one nonproteinaceous polymer is a polyethylene glycol (PEG).

15 19. The conjugate of claim 18 wherein the PEG has an average molecular weight of at least about 20 kD.

20 20. The conjugate of claim 19 wherein the PEG has an average molecular weight of at least about 40 kD.

21. The conjugate of claim 19 wherein the PEG is a single chain molecule.

22. The conjugate of claim 20 wherein the PEG is a branched chain molecule.

25 23. The conjugate of claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is a F(ab')₂ and is covalently attached to no more than about 2 PEG molecules.

24. The conjugate of claim 19, wherein the conjugate contains no more than one antibody fragment, and wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH and is covalently attached to no more than one PEG molecule.

5 25. The conjugate of claim 24 wherein the PEG molecule is covalently attached to the hinge region of the antibody fragment.

26. The conjugate of claim 1, wherein the conjugate contains no more than one antibody fragment, wherein the antibody fragment is selected from the group consisting of Fab, Fab' and Fab'-SH, wherein the antibody fragment is covalently attached to no more than one nonproteinaceous polymer molecule, and wherein the nonproteinaceous polymer molecule is a polyethylene glycol (PEG) having an average molecular weight of at least about 20 kD.

27. The conjugate of claim 26 wherein the PEG has an average molecular weight of at least about 30 kD.

28. The conjugate of claim 27 wherein the PEG has an average molecular weight of at least about 40 kD.

29. The conjugate of claim 26 wherein the PEG is a single chain molecule.

30. The conjugate of claim 28 wherein the PEG is a branched chain molecule.

31. The conjugate of claim 1 wherein the antibody fragment comprising the antigen binding site is humanized.

32. The conjugate of claim 1 wherein the conjugate contains no more than one antibody fragment.

33. The conjugate of claim 1, wherein the covalent structure of the conjugate is free of any matter other than the antibody fragment and nonproteinaceous polymer molecules that form the conjugate.

34. The conjugate of claim 1, wherein the covalent structure of the conjugate incorporates one or more nonproteinaceous labels, and wherein the covalent structure of the conjugate is free of any matter other than the antibody fragment, nonproteinaceous polymer and nonproteinaceous label molecules that form the conjugate.

35. The conjugate of claim 34 wherein at least one nonproteinaceous label is a radiolabel.

36. A composition comprising the conjugate of claim 1 and a carrier.

37. The composition of claim 36 that is sterile.

38. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human VEGF.

39. A method for inhibiting angiogenesis in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 38.

40. A method for treating a neovascular disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 38.

41. The method of claim 40 wherein the neovascular disorder is tumor vascularization.

42. The method of claim 40 wherein the neovascular disorder is an intraocular neovascular disorder.

5 43. The method of claim 42 wherein the intraocular neovascular disorder is age-related macular degeneration (AMD).

44. A method for inhibiting the growth of tumor cells in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 38.

10 45. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to HER2.

46. A method for inhibiting the growth of a HER-2 expressing cancer cell in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 45.

47. The method of claim 46 wherein the cancer cell overexpresses HER2.

20 48. A method of treating a patient having a tumor that overexpresses HER2 comprising administering to the patient the conjugate of claim 45 in an amount effective to reduce the patient's tumor burden.

49. The method of claim 48 wherein the tumor is a breast cancer.

50. A method of binding the conjugate of claim 45 to a human cell expressing HER2, comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to HER2 on the cell surface.

5 51. The method of claim 50 wherein the cell is a tumor cell.

52. The method of claim 51 wherein the tumor cell overexpresses HER2.

10 53. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human CD20.

54. A method of inhibiting the growth of a neoplastic cell expressing CD20 in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 54.

55. The method of claim 54 wherein the cell is a B lymphocyte.

56. A method of treating a CD20-expressing lymphoma in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 53.

57. The method of claim 56 wherein the lymphoma is a B lymphocytic lymphoma.

25 58. A method of binding the conjugate of claim 53 to a human cell expressing CD20, comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to CD20 on the cell surface.

59. The method of claim 58 wherein the cell is a B lymphocyte.

60. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human CD18.

61. A method of treating an inflammatory disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 60.

62. The method of claim 61 wherein the inflammatory disorder is an ischemic reperfusion disorder.

63. The method of claim 62 wherein the ischemic reperfusion disorder is acute myocardial infarction.

64. The method of claim 62 wherein the ischemic reperfusion disorder is stroke.

65. A method of treating an immune disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 60.

66. The method of claim 65 wherein the immune disorder is graft rejection in a transplant recipient.

67. A method of binding the conjugate of claim 60 to a human cell expressing CD18, comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to CD18 on the cell surface.

68. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human CD11a.

69. A method of treating an inflammatory disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 68.

70. The method of claim 69 wherein the inflammatory disorder is psoriasis.

71. A method of treating an immune disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 68.

72. The method of claim 71 wherein the immune disorder is graft rejection in a transplant recipient.

73. The method of claim 71 wherein the immune disorder is multiple sclerosis.

74. A method of treating asthma in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 68.

75. A method of binding the conjugate of claim 68 to a human cell expressing CD11a comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to CD11a on the cell surface.

76. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human IgE.

77. The conjugate of claim 76 comprising at least one antibody fragment having an antigen binding site that binds to membrane-bound IgE on human B-lymphocytes but does not bind to soluble IgE bound to Fc ϵ RI receptor on human basophils.

78. A method of treating an IgE-mediated disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 77.

79. The method of claim 78 wherein the IgE-mediated disorder is an allergic disease.

80. The method of claim 79 wherein the allergic disease is allergic rhinitis.

81. The method of claim 79 wherein the allergic disease is allergic asthma.

82. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human Apo-2 receptor.

83. The conjugate of claim 82 wherein the anti-human Apo-2 receptor antibody fragment is an Apo-2 receptor agonist.

84. A method of treating cancer in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 83.

85. The method of claim 84 wherein the cancer is colon cancer.

86. A method for inducing apoptosis of a human cell expressing Apo-2 receptor comprising contacting the cell with the conjugate of claim 83 under conditions wherein the conjugate induces apoptotic death of the cell.

87. The method of claim 86 wherein the cell is a cancer cell.

88. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human TNF- α .

89. A method of treating an inflammatory disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 88.

90. The method of claim 89 wherein the inflammatory disorder is Crohn's disease.

91. The method of claim 89 wherein the inflammatory disorder is inflammatory bowel disease.

92. The method of claim 89 wherein the inflammatory disorder is rheumatoid arthritis.

93. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human tissue factor.

94. A method for treating a thrombotic disease in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 93.

95. The method of claim 94 wherein the thrombotic disease is deep vein thrombosis.

96. The method of claim 94 wherein the thrombotic disease is arterial thrombosis.

97. A method for inhibiting blood coagulation in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 93.

98. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human GPIIb-IIIa integrin.

99. A method for treating a thrombotic disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 98.

100. The method of claim 99 wherein the thrombotic disorder is vascular restenosis.

101. The method of claim 99 wherein the thrombotic disorder is unstable angina.

102. A method of binding the conjugate of claim 98 to a human cell expressing GPIIb-IIIa integrin comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to the cell.

103. The method of claim 102 wherein the cell is a platelet.

104. A method for inhibiting platelet aggregation in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 98.

105. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human $\alpha_4\beta_7$ integrin.

106. A method of treating an inflammatory disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 105.

107. The method of claim 106 wherein the inflammatory disorder is inflammatory bowel disease (IBD).

108. A method of binding the conjugate of claim 105 to a human cell expressing $\alpha_4\beta_7$ comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to the cell.

109. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human EGFR.

5 110. A method of treating cancer in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 109.

111. A method of inhibiting the growth of a cancer cell in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 109.

10 112. A method of binding the conjugate of claim 109 to a human cell expressing EGFR comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to the cell.

113. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human CD3.

114. A method of treating an immune disorder in a mammal administering to the mammal an effective amount of the conjugate of claim 113.

115. The method of claim 114 wherein the immune disorder is graft rejection in a transplant recipient.

116. A method of binding the conjugate of claim 113 to a human cell expressing CD3
25 comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to the cell.

117. The method of claim 116 wherein the cell is a T lymphocyte.

118. The conjugate of any of claims 1-35 comprising at least one antibody fragment having an antigen binding site that binds to human interleukin-2 receptor α -chain (TAC).

5 119. A method of treating an immune disorder in a mammal comprising administering to the mammal an effective amount of the conjugate of claim 118.

120. The method of claim 119 wherein the immune disorder is graft rejection in a transplant recipient.

10 121. The method of claim 120 wherein the graft rejection is kidney graft rejection.

122. A method of binding the conjugate of claim 118 to a human cell expressing TAC comprising contacting the cell with the conjugate under conditions wherein the conjugate binds to the cell.

123. The method of claim 122 wherein the cell is a T or B lymphocyte.

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